(FILE 'HOME' ENTERED AT 11:49:28 ON 18 MAR 2003)

FILE 'BIOSIS, MEDLINE, CAPLUS, EMBASE, CANCERLIT' ENTERED AT 11:49:39 ON 18 MAR 2003

L1	1374	PHOSPHATE REABSORPTION
L2	0	PHOSHPATE RE-ABSORPTION
L3	10	FRP-4
L4	371	FRIZZLED RELATED PROTEIN
L5	6	FRZB2
L6	2	DDC4
L7	0	L1 AND L3
L8	0	L1 AND L4
L9	0	L1 AND L5
L10	0	L1 AND L6
L11	79	PHOSPHATONIN
L12	11	L11 AND L1
L13	4	DUP REM L12 (7 DUPLICATES REMOVED)
L14	3630	FRP
L15	1	L1 AND L14
L16	1297	PHOSPHATURIC
L17	154	L1 AND L16
L18	1	L3 AND L16
L19	4	L4 AND L16
L20	2	DUP REM L19 (2 DUPLICATES REMOVED)
L21	0	L5 AND L16
L22	0	L6 AND L16

L13 ANSWER 1 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
ACCESSION NUMBER: 2002:478909 BIOSIS
DOCUMENT NUMBER: PREV200200478909
TITLE: Fibroblast growth factor (FGF)-23 inhibits renal **phosphate reabsorption** by activation of the mitogen-activated protein kinase pathway.
AUTHOR(S): Yamashita, Tetsuo; Konishi, Morichika; Miyake, Ayumi; Inui, Ken-Ichi; Itoh, Nobuyuki (1)
CORPORATE SOURCE: (1) Department of Genetic Biochemistry, Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo, Kyoto, 606-8501: itohnobu@pharm.kyoto-u.ac.jp Japan
SOURCE: Journal of Biological Chemistry, (August 2, 2002) Vol. 277, No. 31, pp. 28265-28270. http://www.jbc.org/. print. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The homeostasis of the plasma phosphate level is essential for many biological processes including skeletal mineralization. The reabsorption of phosphate in the kidney is a major determinant of the plasma levels of phosphate. **Phosphatonin** is a hormone-like factor that specifically inhibits phosphate uptake in renal proximal epithelial cells. Recent studies on tumor-induced osteomalacia suggested that **phosphatonin** was potentially identical to fibroblast growth factor (FGF)-23. However, as purified recombinant FGF-23 could not inhibit phosphate uptake in renal proximal epithelial cells, the mechanism of action of FGF-23 remains to be elucidated. Therefore, we examined the mechanism of action of FGF-23 in cultured renal proximal epithelial cells, opossum kidney cells. FGF-23 was found to require heparin-like molecules for its inhibitory activity on phosphate uptake. FGF-23 binds to the FGF receptor 3c, which is mainly expressed in opossum kidney cells, with high affinity. An inhibitor for tyrosine kinases of the FGF receptor, SU 5402, blocked the activity of FGF-23. FGF-23 activated the mitogen-activated protein kinase (MAPK) pathway, which is the major intracellular signaling pathway of FGF. Inhibitors of the MAPK pathway, PD98059 and SB203580, also blocked the activity of FGF-23. The present findings have revealed a novel MAPK-dependent mechanism of the regulation of phosphate uptake by FGF signaling.

L13 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 2001:383764 BIOSIS
DOCUMENT NUMBER: PREV200100383764
TITLE: FGF-23 inhibits renal tubular phosphate transport and is a PHEX substrate.
AUTHOR(S): Bowe, Ann E.; Finnegan, Richard; de Beur, Suzanne M. Jan; Cho, Justin; Levine, Michael A.; Kumar, Rajiv; Schiavi, Susan C. (1)
CORPORATE SOURCE: (1) Genzyme, 1 Mountain Road, Framingham, MA, 01701-9322: susan.schiavi@genzyme.com USA
SOURCE: Biochemical and Biophysical Research Communications, (June 22, 2001) Vol. 284, No. 4, pp. 977-981. print. ISSN: 0006-291X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Oncogenic osteomalacia (OOM), X-linked hypophosphatemia (XLH), and autosomal dominant hypophosphatemic rickets (ADHR) are phenotypically similar disorders characterized by hypophosphatemia, decreased renal **phosphate reabsorption**, normal or low serum calcitriol concentrations, normal serum concentrations of calcium and parathyroid hormone, and defective skeletal mineralization. XLH results from mutations in the PHEX gene, encoding a membrane-bound endopeptidase, whereas ADHR is associated with mutations of the gene encoding FGF-23. Recent evidence that FGF-23 is expressed in mesenchymal tumors associated with OOM suggests that FGF-23 is responsible for the phosphaturic activity

previously termed "**phosphatonin**." Here we show that both wild-type FGF-23 and the ADHR mutant, FGF-23(R179Q), inhibit phosphate uptake in renal epithelial cells. We further show that the endopeptidase, PHEX, degrades native FGF-23 but not the mutant form. Our results suggest that FGF-23 is involved in the pathogenesis of these three hypophosphatemic disorders and directly link PHEX and FGF-23 within the same biochemical pathway.

L13 ANSWER 3 OF 4 MEDLINE
ACCESSION NUMBER: 2002053124 MEDLINE
DOCUMENT NUMBER: 21637562 PubMed ID: 11778363
TITLE: [Familiar hypophosphatemic rickets].
Familiaris hypophosphataemias rachitis.
AUTHOR: Reusz G
CORPORATE SOURCE: Altalanos Orvostudomanyi Kar, I. sz. Gyermekklinika, Semmelweis Egyetem, Budapest.. reusz@gyerl.sote.hu
SOURCE: ORVOSI HETILAP, (2001 Dec 2) 142 (48) 2659-65. Ref: 41
Journal code: 0376412. ISSN: 0030-6002.
PUB. COUNTRY: Hungary
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Hungarian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020405
Entered Medline: 20020404

AB Familiar hypophosphatemic rickets (FHR) is characterized by isolated defect of renal **phosphate reabsorption**, hypophosphataemia, rickets and poor growth. In untreated cases parathyroid hormone and calcitriol levels are normal. FHR is caused by mutations of the PHEX gene encoding a zinc-binding metalloprotease enzyme. PHEX is expressed in bones and the parathyroid gland but not in the kidney. The gene product is involved in the inactivation of a phosphate regulating hormone (**phosphatonin**). The presence of this hormone through unknown mechanisms decreases the sodium-dependent phosphate cotransporter in the kidney resulting in impaired phosphate transport. In addition the PHEX gene product exerts autocrine and paracrine effects on the bone. Despite recent advances in the understanding of the pathomechanism, treatment of FHR is still symptomatic. It consists of active vitamin D analogues and oral phosphate supplementation. Nephrocalcinosis is a well-known, usually non-progressive side effect of the conventional therapy. As shown by pilot studies, poorly growing children with FHR may benefit from the positive effect of human recombinant growth hormone (rhGH). However, rhGH treatment could aggravate the already existing tendency to disproportionate growth resulting in the overgrowth of the trunk. The disturbed phosphate homeostasis persists during the whole life span of the FHR patients. It is therefore essential to provide lifelong care, to prevent late skeletal and dental consequences or to treat them if already established. That care should be done by the teamwork of the pediatrician, internist, orthopedist, dentist and the psychologist.

L13 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:580342 CAPLUS
DOCUMENT NUMBER: 135:286097
TITLE: Molecular aspects of phosphate homeostasis in mammals
AUTHOR(S): Beck, L.; Silve, C.
CORPORATE SOURCE: INSERM U 426 et Institut federatif de recherche .mchlt. Cellules Epitheliales .mchgt., Faculte de medecine Xavier Bichat, Paris, Fr.
SOURCE: Nephrologie (2001), 22(4), 149-159
CODEN: NEPHDY; ISSN: 0250-4960
PUBLISHER: Medecine et Hygiene

DOCUMENT TYPE: Journal; General Review
LANGUAGE: French

AB A review with refs. Renal **phosphate reabsorption**, the major determinant of phosphate homeostasis, is primarily dependent on dietary phosphate content and multiple hormonal factors. Over the last few years, the identification of sodium-dependent phosphate transporters in kidney, intestine and bone, as well as new insights into the mol. mechanisms involved in several hereditary hypophosphatemias, allow to set up novel **phosphate reabsorption** regulatory pathways.
This review describes mol. players involved in these mechanisms, summarizes phosphate transport data in kidney, intestine and bone, and describes recent findings concerning the three most common hereditary hypophosphatemias.

REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 1 OF 1 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 75063246 EMBASE
DOCUMENT NUMBER: 1975063246
TITLE: Mechanism of the blunted phosphaturia in saline loaded thyroparathyroidectomized dogs.
AUTHOR: Beck L.H.; Goldberg M.
CORPORATE SOURCE: Ren. Electrol. Sect., Dept. Med., Univ. Pennsylvania Sch. Med., Philadelphia, Pa., United States
SOURCE: Kidney International, (1974) 6/1 (18-23).
CODEN: KDYIA5
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
028 Urology and Nephrology
003 Endocrinology
LANGUAGE: English

AB To define the relationships between sodium and phosphate transport in the presence and absence of parathyroid hormone (PTH), and to evaluate the effects of saline loading on these relationships, recollection micropuncture studies were done in proximal tubules of intact and thyroparathyroidectomized (TPTX) dogs. Micropuncture collections were made before and after 5% of body wt saline expansion (SE) in three groups of dogs: intact (N=6), acute TPTX (N=6) and 24 hr TPTX (N=6). Before SE, proximal tubular fluid/ultrafiltrate phosphate ratio [(TF/UF)p] was 0.62.+-.0.05 in intact dogs and was unrelated to tubular fluid/plasma inulin ratio [(TF/P)In]. In both TPTX groups (TF/UF)p varied inversely with (TF/P)In (P<0.001). In late proximal tubules [(TF/P)In>1.70], (TF/UF)p was 0.39 in acute TPTX and 0.40 in 24 hr TPTX. After SE, (TF/UF)p rose to values of 0.7 to 0.8 in all three groups. (TF/P)In fell in all animals after SE so that fractional reabsorption of phosphate (**FRP**) in the proximal tubule fell markedly. The decrement in **FRP** was equivalent in all three groups: 0.29 in intact, 0.34 in acute TPTX and 0.34 in 24 hr TPTX. A significant phosphaturia (0.26 of filtered load) occurred only in intact animals, despite equivalent natriuresis in all three groups. The authors conclude that SE causes equivalent inhibition of proximal **phosphate reabsorption** in both intact and TPTX dogs. In intact dogs, the portion of proximal tubular phosphate inhibited by SE is almost totally excreted. In TPTX animals, enhanced **phosphate reabsorption** beyond the cortical proximal tubule accounts for the blunted phosphaturia.

L18 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:461775 CAPLUS
DOCUMENT NUMBER: 137:276731
TITLE: Tumors associated with oncogenic osteomalacia express genes important in bone and mineral metabolism
AUTHOR(S): Jan De Beur, Suzanne M.; Finnegan, Richard B.; Vassiliadis, John; Cook, Brian; Barberio, Dana; Estes, Scott; Manavalan, Partha; Petroziello, Joseph; Madden, Stephen L.; Cho, Justin Y.; Kumar, Rajiv; Levine, Michael A.; Schiavi, Susan C.
CORPORATE SOURCE: Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
SOURCE: Journal of Bone and Mineral Research (2002), 17(6), 1102-1110
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: American Society for Bone and Mineral Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Oncogenic osteomalacia (OOM) is assocd. with primitive mesenchymal tumors that secrete **phosphaturic** factors resulting in low serum concns. of phosphate and calcitriol, phosphaturia, and defective bone mineralization. To identify overexpressed genes in these tumors, the authors compared gene expression profiles of tumors resected from patients with OOM and histol. similar control tumors using serial anal. of gene expression (SAGE). Three hundred and sixty-four genes were expressed at least twofold greater in OOM tumors compared with control tumors. A subset of 67 highly expressed genes underwent validation with an extended set of OOM and control tumors using array anal. or reverse-transcription polymerase chain reaction (RT-PCR). Ten of these validated genes were consistently overexpressed in all OOM tumors relative to control tumors. Strikingly, genes with roles in bone matrix formation, mineral ion transport, and bone mineralization were highly expressed in the OOM tumors.

L20 ANSWER 1 OF 2 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002430237 MEDLINE
DOCUMENT NUMBER: 22174470 PubMed ID: 12187320
TITLE: New insights into phosphate homeostasis: fibroblast growth factor 23 and **frizzled-related protein**-4 are **phosphaturic** factors derived from tumors associated with osteomalacia.
AUTHOR: Kumar Rajiv
CORPORATE SOURCE: Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, Minnesota 55905, USA.. rkumar@mayo.edu
CONTRACT NUMBER: AR27032 (NIAMS)
DK25409 (NIDDK)
DK58546 (NIDDK)
DK59505 (NIDDK)
SOURCE: CURRENT OPINION IN NEPHROLOGY AND HYPERTENSION, (2002 Sep) 11 (5) 547-53. Ref: 78
Journal code: 9303753. ISSN: 1062-4821.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20020821
Last Updated on STN: 20030222
Entered Medline: 20030221

AB PURPOSE OF REVIEW: Studies of patients with tumors associated with osteomalacia (tumor-induced osteomalacia), X-linked hypophosphatemia (XLH) and autosomal-dominant hypophosphatemic rickets have provided important new insights into the identity and mechanisms of action of factors that play a role in controlling renal phosphate excretion and serum phosphate concentrations. In the present review I discuss how these disorders may be mechanistically related to one another. RECENT FINDINGS: Patients (or mice) with these disorders manifest rickets as a result of excessive urinary phosphate losses. Tumors associated with osteomalacia elaborate factors ('phosphatonins') that increase renal phosphate excretion and reduce serum phosphate concentrations. These factors include fibroblast growth factor (FGF) 23 and **frizzled-related protein**-4. Mice with XLH (Hyp) elaborate a circulating factor that induces changes in mineral metabolism similar to those in patients with tumor-induced osteomalacia. In mice and humans with XLH, a mutant enzyme, phex/PHEX, cannot degrade the **phosphaturic** factor. Patients with autosomal-dominant hypophosphatemic rickets produce a mutant FGF 23 that is resistant to proteolytic degradation. Excessive FGF 23 activity is associated with increased renal phosphate excretion and hypophosphatemia. SUMMARY: In tumor-induced osteomalacia, excessive production of factors such as FGF 23 and **frizzled-related protein**-4 is associated with inability of endogenous proteolytic enzymes to degrade these individual substances, with resultant hyperphosphaturia, hypophosphatemia, and rickets. In XLH, mutant PHEX/phex (phosphate-regulating gene with homology to endopeptidases located on the X-chromosome) activity prevents degradation of a **phosphaturic** factor. In autosomal-dominant hypophosphatemic rickets, a mutant form of FGF 23 that is resistant to proteolytic degradation causes increased renal phosphate losses and hypophosphatemia.

L20 ANSWER 2 OF 2 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002359281 MEDLINE
DOCUMENT NUMBER: 22097723 PubMed ID: 12105393
TITLE: Phosphatonins: a new class of phosphate-regulating proteins.
AUTHOR: Schiavi Susan C; Moe Orson W

CORPORATE SOURCE: Applied Genomics, Genzyme Corporation, One Mountain Road, Framingham, Massachusetts 01701, USA..
susan.schiavi@genzyme.com
CONTRACT NUMBER: P01-DK20543 (NIDDK)
R01-48482
R01-54396
SOURCE: CURRENT OPINION IN NEPHROLOGY AND HYPERTENSION, (2002 Jul) 11 (4) 423-30. Ref: 72
Journal code: 9303753. ISSN: 1062-4821.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20020710
Last Updated on STN: 20021217
Entered Medline: 20021204
AB PURPOSE OF REVIEW: There is an intimate relationship between phosphate and calcium homeostasis throughout the animal kingdom. One traditional assumption is that all phosphate-regulating hormones are primarily calcium-regulating hormones. Although the notion of a circulating substance dedicated to phosphate homeostasis has existed for more than a decade, it is not until recently that these hormones have been identified. The molecular characterization of these substances will prove to be critical for understanding phosphate physiology and clinical disorders of phosphate metabolism. RECENT FINDINGS: This review will focus primarily on the first two proteins recently shown to have phosphatonin properties. Using three human diseases as models and a combination of positional cloning and differential gene expression, fibroblast growth factor 23 and **frizzled-related protein** 4 were shown to be associated with one or more of these diseases. Although both of these substances have **phosphaturic** action, their biological effects are likely to extend beyond epithelial phosphate transport. SUMMARY: The phosphatonins are a growing family of substances that may act on multiple organs in autocrine, paracrine, and endocrine modes to regulate phosphate metabolism. As this list expands, the need for a more rigid definition of the term phosphatonin becomes evident. The identification and characterization of these phosphate-regulatory compounds will provide a clearer understanding of how individual phosphatonins regulate phosphate in normal and disease physiology.